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Triarylalkenes from the site-selective reductive cross-coupling of benzophenones and aldehydes†

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PhP(Li)TMS converts benzophenones to phosphaalkenes which upon activation under oxidizing, basic conditions react with aromatic aldehydes under the formation of triarylalkenes. The one-pot reaction omits transition metals, proceeds at room temperature and precludes the formation of any homo-coupling products. Systematic substrate variations reveal reactivity patterns that are useful for the identification of ketone/aldehyde combinations that can be coupled in yields up to 80%.

The C=C double bond is one of the fundamentally most important functional groups in organic chemistry. It possesses high synthetic versatility,[1] gives compounds rigidity, and as a structural motif, is at the heart of π-conjugation.[2] One access to C=C double bonds is through the direct reductive coupling of two C=O containing compounds. This chemistry was pioneered in the 1970s by McMurry who discovered that low-valent Ti species that are produced *in situ* from $TiCl_4$ and reductants such as Zn and Cu, can reduce aldehydes and ketones.[3] The thereby produced Ti-coordinated ketyl radicals can couple to each other with the Ti species acting as oxygen acceptor, finally leading to TiO_2 and the desired alkenes.[4] Although the reaction is often described as "tricky" in textbooks,[5] it has been the only available method in the literature for the reductive coupling of two carbonyl compounds. In addition to the harsh reaction conditions, the incompatibility with easily reducible functional groups and the difficult practical handling,[6] the biggest drawback of the McMurry coupling is its lack of site selectivity, and the intermolecular reductive coupling of two different carbonyl compounds of similar reactivity to form unsymmetric alkenes is largely impossible.[7] Instead, a statistic mixture of the three different alkene products can be expected.[8] It was not until two years ago that conceptually new strategies for the selective formation of unsymmetric alkenes from two different carbonyl compounds have started to emerge. Li and co-workers published a Ru-catalyzed process in which hydrazine acts as reductant and oxygen acceptor.[9] At the same time, we reported the first transition metal-free, site-selective coupling of two aldehydes to alkenes,[10] in which site-selectivity is achieved by the sequential addition of the carbonyl compounds at different stages of the one-pot reaction. The reaction proceeds by an ionic mechanism, and occurs at room temperature in less than one hour.

It starts with the conversion of a first aldehyde (generally depicted as a carbonyl compound in Fig. 1) to a phosphaalkene using a suitable coupling reagent.[11] In stage 2, the $\lambda^3\sigma^2$-phosphorus in the phosphaalkene is converted to a $\lambda^5\sigma^4$ derivative, which bears resemblance to commonly used olefination reagents.[12] The latter will thus react with a second carbonyl compound to form the desired olefin (stage 3).[13]

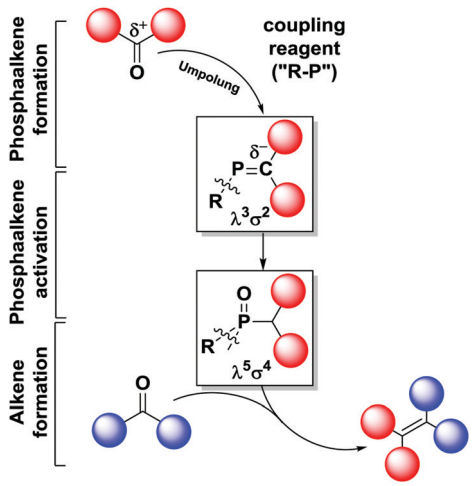

Fig. 1 Schematic presentation of the mechanistic steps behind the coupling protocol: a carbonyl compound (red) is converted to a phosphaalkene intermediate under Umpolung of the polarity of the carbonyl carbon. Phosphaalkene activation gives rise to a $\lambda^5\sigma^4$ species which will engage in the coupling step with a second carbonyl compound (blue) to form the olefin product.

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As the reaction proceeds under basic conditions, carbonyl compounds with acidic α-protons are generally problematic due to competing aldol pathways. To this end, we have developed and reported reagents and activation procedures for the coupling of mainly aromatic aldehydes, irrespective of their electronic nature.[10,14] The reductive coupling of aldehydes to ketones to generate trisubstituted alkenes has remained largely elusive.[14b] In the present paper, we report the first example of a reagent that broadly promotes this chemistry, and demonstrate its potential for the reductive coupling of benzophenones and aromatic aldehydes to triarylalkenes.

The cross-coupling sequence in Fig. 1 can be hampered by mainly two factors: the stability of the phosphaalkene intermediate and the propensity of the $\lambda^5\sigma^4$ species to react with the second carbonyl compound. Both aspects correlate inversely with the steric demand of the *P*-substituent, with large groups giving kinetic stabilization to the phosphaalkenes while also decreasing the reactivity of the $\lambda^5\sigma^4$ species. Reagents that have been reported thus far are based on super-mesityl (Mes* = 2,4,6-^{t}Bu$_3$Ph) and mesityl (Mes) *P*-substituents.[15] For the design of a more reactive reagent, we hypothesized that a phenyl group could be a step forward in that it may still stabilize phosphaalkenes, but also lend high reactivity to the $\lambda^5\sigma^4$ species. The change from Mes to phenyl might appear as a minor alteration at first, but it is important to realize that this modification comes with a substantial increase in reactivity at all stages of the sequence, and is synthetically far from trivial.[16] To counter-balance the potentially problematic low kinetic stabilization by the *P*-phenyl-group, we decided to use ketones as the first carbonyl compound in the sequence as trisubstituted phosphaalkenes are generally more stable than disubstituted ones.[17] The envisaged reaction sequence would make the need a virtue in that the ketone, *i.e.*, the hitherto elusive reaction partner, is used to structurally stabilize one of the intermediates, thereby enabling the overall reaction.

Lithiated phenyl(trimethylsilyl)phosphane (PhP(TMS)Li) was identified as the most suitable coupling reagent as it can be prepared easily from PhP(TMS)$_2$ and is known to engage in phospha-Peterson reactions to form phosphaalkenes.[18] In a procedure that was slightly modified compared to literature precedence,[19] ethereal solutions of PhP(TMS)Li that were obtained by the lithium ethoxide – promoted selective removal[20] of one TMS group from PhP(TMS)$_2$ were treated with ketones **A–G**. A diagnostic colour change from light yellow to dark blue was observed in all cases and the reaction is completed within a few minutes. Phosphaalkene formation can be followed by the disappearance of the ^{31}P NMR signal of the starting lithium salt at −143 ppm and the appearance of the characteristic signals of phosphaalkenes **1A–E** at downfield chemical shift (+234 ppm for **1A**, see Fig. 2).[19,21] **1F** that contains only two aryl substituents is kinetically too unstable and polymerizes under the reaction conditions. Such intermediates can however be stabilized to some extent through conjugative effects, for example by the presence of an electron-rich *C*-substituent, which stabilizes the corresponding phosphaalkene **1G**. In general, the phosphaalkenes described herein are designed to be highly reactive, and lack exhaustive kinetic stabilization. Consequently, reaction times need

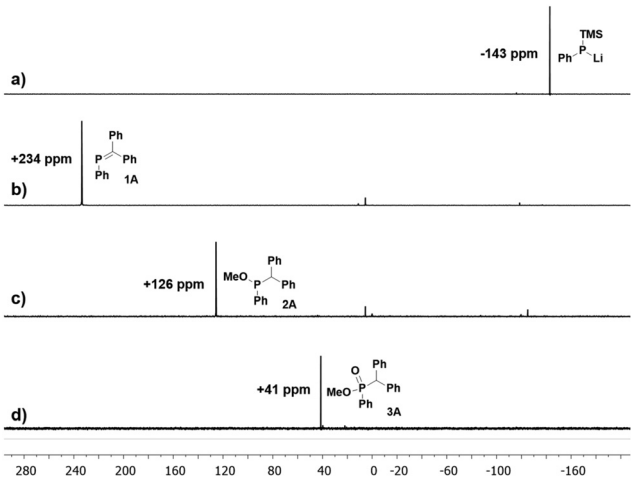
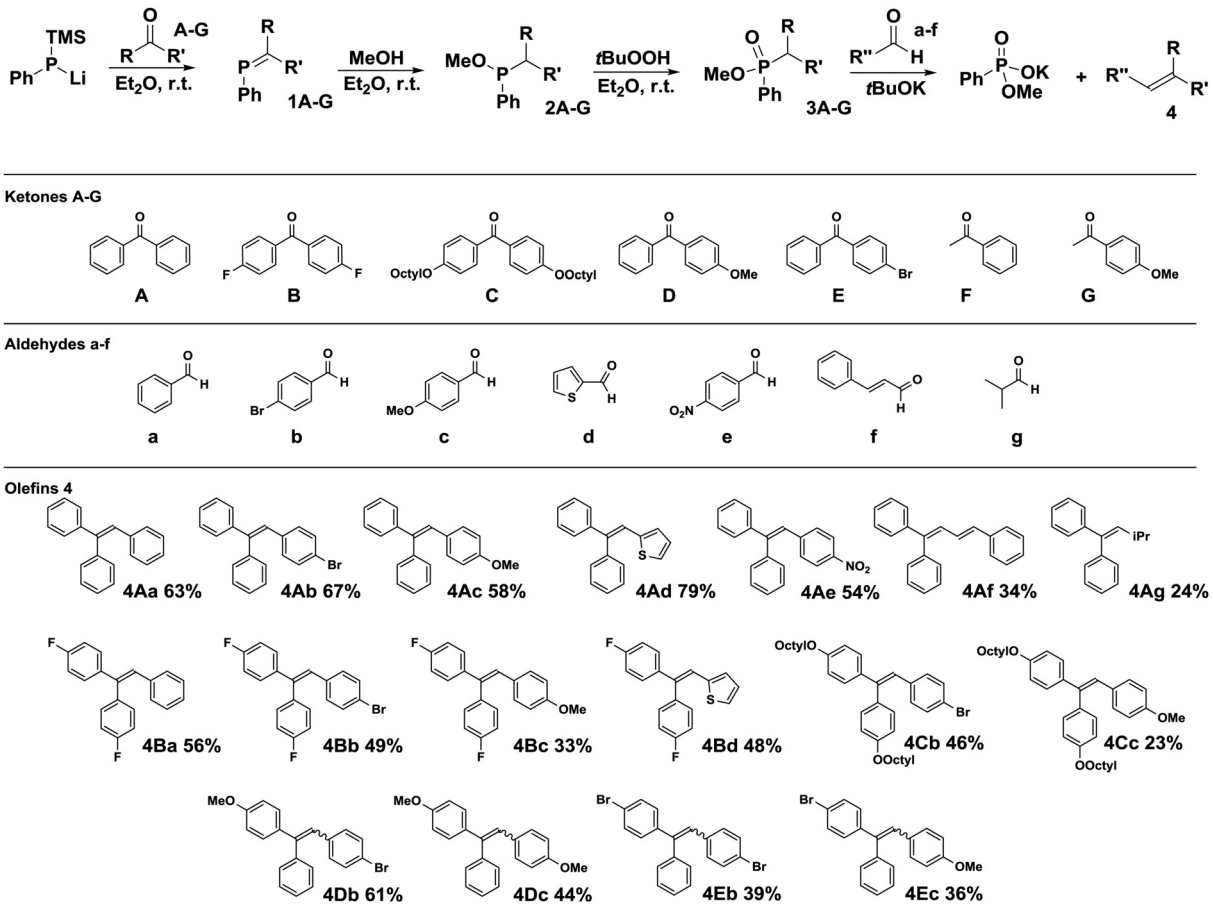


Fig. 2 ^{31}P NMR spectra (in Et_2O) of PhP(TMS)Li (a); the reaction mixtures after addition of carbonyl A (b), followed by methanol (c) and *t*BuOOH (d).

to be kept short. Thus, addition of methanol to the reaction mixture[22] only 1–3 minutes after ketone addition gives rise to compounds **2** (^{31}P chemical shift of 126 ppm for **2A**, Fig. 2). Oxidation of **2** to the corresponding $\lambda^5\sigma^4$ phosphinate **3** can conveniently be achieved by a water-free solution of *t*BuOOH, and is complete after several minutes. Thus, the whole sequence from (PhP(TMS)Li) to **3** is done at room temperature within less than 10 minutes. Phosphinates **3** have a characteristic ^{31}P chemical shift of *ca.* 41 ppm (Fig. 2) and are obtained as white powders after solvent removal. When isolated, the yields for compounds **3** range from 60% for those of electron-deficient ketones (63% for **3B**) to quantitative for electron-rich analogues (quantitative and 97% for **3C** and **3A**, respectively).

Without any further purification, phosphinates **3A–E, G** are dissolved in THF and reacted with aldehydes **a–g** in the presence of a slight excess of potassium *tert*-butoxide. It is important that this step is performed under oxygen free conditions since the anionic form of **3** is prone to oxidative cleavage of the diphenyl methylene substituent under the formation of the corresponding ketone.[22] The reaction times and temperatures vary markedly depending on the electronic nature of the carbonyl compounds to be coupled. If both carbonyl components carry electron-withdrawing substituents (for example **4Bb** and **4Bd** in Scheme 1), the reaction proceeds at room temperature within minutes. For the coupling of electron neutral or slightly electron-rich ketones to aldehydes, the reaction time increases to 15–30 minutes, while in case of two electron-rich coupling partners as in **4Cb** and **4Cc**, even longer times or elevated temperatures are required. Phosphinate **3G** that originates from *p*-methoxyacetophenone **G** does not react with any aldehyde, even when heated to reflux for extended periods of time. Interestingly, also no decomposition to starting acetophenone (due to oxidation) or reductive cleavage under ethylanisole formation is observed, suggesting that the lack of reactivity is due to insufficient acidity of the proton in α-position to the P-center.

The overall yields for the entire one-pot reaction can approach 80% in case of certain substrate combinations. High yields are generally obtained for the coupling of electron neutral ketones



Scheme 1 Trisubstituted alkenes from the one-pot reductive cross-coupling sequence between ketones and aldehydes.

with any aldehyde (for example **4Aa**, **4Ab** and **4Ad**, Scheme 1) or for slightly electron donating ketones such as **D** with neutral and electron-deficient aldehydes (**4Db** and **4Dc**, Scheme 1). Noteworthy is also the formation of **4Ae** with the nitro-substituent, as substrates with this functional group cannot be employed the McMurry coupling due to the radical nature of the latter. As expected, aliphatic (**g**) or conjugated (**f**) aldehydes result in lower yields (*vide supra*). In fact, it is remarkable that *e.g.*, **4Af** is formed at all, as its formation proofs that the last step of the coupling sequence can kinetically compete with aldol condensations. The coupling products from unsymmetric benzophenones (**D** and **E**) do not show any selectivity for the formation of a particular alkene isomer.

The observed trends in reactivity and product yields can be rationalized on grounds of the following considerations. As described above, the yields for phosphinates **3** are higher for electron-rich and -neutral ketones, approaching quantitative formation as in case of **3C**. Assuming that methanol addition to the P=C double bond and oxidation of **2** to **3** are quantitative transformations, this difference in yield directly reflects a difference in yields of the phosphaalkene (**1**) precursors. Thus, phosphaalkenes of electron-rich or -neutral ketones form in higher yields than those of electron-deficient ketones. This reactivity of the first step of the sequence sets an upper limit on the expectable total yield.

Taken this limitation into account, it is possible to deduce a reactivity trend also for the other key step of the sequence, *i.e.*, the reaction of deprotonated **3** with aldehydes. For example, considering that **3A** is formed in almost quantitative yield (97%), the overall yield for the coupling with aldehyde **a** to form **3Aa** (63%) is somewhat modest. On the other hand, phosphinate **3B** that is formed with an initial yield of 63% couples with the same aldehyde **a** under the formation of **3Ba** in an overall yield of 56%, which means that the last step of the sequence proceeds with very high efficacy. Thus, phosphinates **3** that stem from electron deficient ketones are more efficient in the coupling step with aldehydes. The reactivity of the final olefin formation is thus paralleled with the acidity of the proton in α-position to the P-center in **3** which is higher for phosphinates with electron-withdrawing substituents.

Summarizing these observations, it emerges that the formation of phosphinates **3** and their coupling to aldehydes have opposite reactivity patterns in that for example electron-rich benzophenones give rise to high yields of **3** which however react more sluggishly with aldehydes. Conversely, phosphinates of electron-deficient benzophenones form in lower yields, react however very efficiently with aldehydes.

In addition, the observed overall yields also contain a contribution that is attributable to the electronic nature of the aldehyde that is used in the alkene formation stage. When

comparing entries **4Aa–4Ad** or **4Ba–4Bd**, it emerges that identical phosphinates give rise to higher olefin yields for the more electron-deficient aldehyde coupling partners. This reactivity is expectable as such aldehydes are better electrophiles, react faster, and thus leave less time for unwanted side reactions to occur.

In conclusion, we have developed a new one-pot methodology that allows the reductive cross-coupling of benzophenones and aromatic aldehydes to triarylalkenes for the first time. Homo-coupling products which would be encountered in McMurry couplings are not observed at any point of the chemistry, and substrates that are not compatible with the McMurry conditions can be used. The direct carbonyl coupling methodology presented herein circumvents the necessity for olefination reagents such as ylides or phosphonates that are typically produced in two to three separate steps in Wittig and HWE chemistry, respectively. As such, the overall yields of typically 60%, approaching 80% for certain substrate combinations, are highly competitive. Mechanistically, the one-pot reaction described herein commences with the formation of a phosphaalkene intermediate which proceeds with an Umpolung of the polarity of the former ketone carbon. Quenching of the phosphaalkene with methanol, followed by P-oxidation gives rise to phosphinates **3**, which react with aldehydes under the formation of the trisubstituted olefins. The procedure is applicable for the coupling of carbonyl compounds that traditionally react sluggishly in Wittig-type olefination reactions, and can be applied for benzophenones with electron-withdrawing as well as electron-donating substituents. A similar broad substrate scope is observed for the aldehydes as long as they do not contain acidic α-protons. Through systematic variations of the substituents on both coupling partners, reactivity patterns are described that allow the identification of substrate combinations that are particularly suitable for the developed methodology, and that promise high yields for the synthesis of future trisubstituted olefins.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry Part B: Reactions and Synthesis*, 5th edn, Springer, New York, 2008.
2 (*a*) M. Klikar, P. Solanke, J. Tydlitát and F. Bureš, *Chem. Rec.*, 2016, **16**, 1886–1905; (*b*) S. R. Marder, D. N. Beratran and L. T. Cheng, *Science*, 1991, **252**, 103–106.
3 J. E. McMurry and M. P. Fleming, *J. Am. Chem. Soc.*, 1974, **96**, 4708–4709.
4 J. E. McMurry, *Chem. Rev.*, 1989, **89**, 1513–1524.
5 L. Kurti and B. Czako, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, San Diego, 2005.
6 (*a*) M. Ephritikhine, *Chem. Commun.*, 1998, 2549–2554; (*b*) J. E. McMurry, *Acc. Chem. Res.*, 1974, **7**, 281–286.
7 J. E. McMurry, M. P. Fleming, K. L. Kees and L. R. Krepski, *J. Org. Chem.*, 1978, **43**, 3255–3266.
8 J. E. McMurry and L. R. Krepski, *J. Org. Chem.*, 1976, **41**, 3929–3930.
9 W. Wei, X.-J. Dai, H. Wang, C. Li, X. Yang and C.-J. Li, *Chem. Sci.*, 2017, **8**, 8193–8197.
10 K. Esfandiarfard, J. Mai and S. Ott, *J. Am. Chem. Soc.*, 2017, **139**, 2940–2943.
11 K. Esfandiarfard, A. I. Arkhypchuk, A. Orthaber and S. Ott, *Dalton Trans.*, 2016, **45**, 2201–2207.
12 (*a*) J. Clayden and S. Warren, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 241–270; (*b*) W. S. Wadsworth, Jr., *Org. React.*, 1977, **25**, 7310; (*c*) O. I. Kolodiazhnyi, *Phosphorus Ylides*, Wiley-VCH, Weinheim, 2007, pp. 359–538.
13 L. Horner, H. Hoffmann, W. Klink, H. Ertel and V. G. Toscano, *Chem. Ber.*, 1962, **95**, 581–601.
14 (*a*) J. Mai, A. I. Arkhypchuk, A. K. Gupta and S. Ott, *Chem. Commun.*, 2018, **54**, 7163–7166; (*b*) A. I. Arkhypchuk, N. D'Imperio and S. Ott, *Org. Lett.*, 2018, **20**, 5086–5089.
15 M. Yoshifuji, *J. Organomet. Chem.*, 2000, **611**, 210–216.
16 (*a*) T. C. Klebach, R. Lourens and F. Bickelhaupt, *J. Am. Chem. Soc.*, 1978, **100**, 4886–4888; (*b*) F. Mathey, *Angew. Chem., Int. Ed.*, 2003, **42**, 1578–1604; (*c*) M. Yoshifuji, *Dalton Trans.*, 1998, 3343–3350.
17 (*a*) A. Marinetti, S. Bauer, L. Ricard and F. Mathey, *Organometallics*, 1990, **9**, 793–798; (*b*) A. Marinetti and F. Mathey, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1382–1384.
18 (*a*) G. Becker, W. Uhl and H. J. Wessely, *Z. Anorg. Allg. Chem.*, 1981, **479**, 41–56; (*b*) T. Van Der Does and F. Bickelhaupt, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1987, **30**, 515–518; (*c*) H. Kawanami, K. Toyota and M. Yoshifuji, *J. Organomet. Chem.*, 1997, **535**, 1–5; (*d*) M. Yam, J. H. Chong, C. W. Tsang, B. O. Patrick, A. E. Lam and D. P. Gates, *Inorg. Chem.*, 2006, **45**, 5225–5234.
19 S. Wang, K. Samedov, S. C. Serin and D. P. Gates, *Eur. J. Inorg. Chem.*, 2016, 4144–4151.
20 (*a*) F. Uhlig and R. Hummeltenberg, *J. Organomet. Chem.*, 1993, **452**, C9–C10; (*b*) U. Englich, K. Hassler, K. Ruhlandt-Senge and F. Uhlig, *Inorg. Chem.*, 1998, **37**, 3532–3537.
21 (*a*) C. W. Tsang, M. Yam and D. P. Gates, *J. Am. Chem. Soc.*, 2003, **125**, 1480–1481; (*b*) R. Appel, F. Knoll and I. Ruppert, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 731–744.
22 T. A. Van der Knaap, T. C. Klebach, R. Lourens, M. Vos and F. Bickelhaupt, *J. Am. Chem. Soc.*, 1983, **105**, 4026–4032.